

## MEETING ABSTRACT

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# Antiepileptic activity and subtype-selective action of flupirtine at GABA<sub>A</sub> receptors

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## Background

Flupirtine is used as analgesic drug with muscle-relaxant properties. In addition, it has been suggested to possess antiepileptic properties. Recently, flupirtine has been revealed to simultaneously act at K<sub>v</sub>7 channels and GABA<sub>A</sub> receptors. Here, antiepileptic activity and underlying mechanisms of action of flupirtine were investigated.

## Methods

We used the patch clamp technique and primary cultures of hippocampal neurons or transfected tsA cells to investigate effects of flupirtine.

## Results

In hippocampal neurons, flupirtine reduced seizure-like activity with no effect at 1 to 3 μM, and maximal effects at 10 to 30 μM; it enhanced currents through K<sub>v</sub>7 channels with EC<sub>50</sub> values at 6 μM. Flupirtine (30 μM) modulated GABA-induced currents in hippocampal neurons by reducing EC<sub>50</sub> values for GABA threefold and maximal current amplitudes by 15%. Hence, flupirtine acted as an uncompetitive antagonist. Flupirtine did not alter rise time, decay time, or amplitudes of miniature inhibitory postsynaptic currents (mIPSCs), but enhanced the bicuculline-sensitive tonic current. When phasic GABAergic inhibition was blocked by penicillin G (5 mM), flupirtine enhanced maximal amplitudes of GABA-evoked currents by 43%, but hardly affected EC<sub>50</sub> values. As these results suggested that flupirtine was able to differentiate between different GABA<sub>A</sub> receptor subtypes, its effects on recombinant GABA<sub>A</sub> receptors were

investigated in tsA cells. With α1β2γ2 receptors, flupirtine reduced EC<sub>50</sub> values for GABA threefold and maximal current amplitudes by 25%; with α1β2 receptors, it reduced EC<sub>50</sub> values for GABA twofold, but reduced maximal current amplitudes by 35%.

## Conclusions

These results indicate that flupirtine (i) exerts antiepileptic activity, (ii) modulates tonic, but not phasic, GABAergic inhibition and blocks K<sub>v</sub>7 channels in hippocampal neurons, and (iii) affects GABA<sub>A</sub> receptors in a subunit-dependent manner.

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